

New regulations regarding e-prescriptions may increase the risk of acute withdrawal syndromes in patients dependent on benzodiazepines or non-benzodiazepine hypnotics

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Summary

The implementation of solutions in the area of e-health and use of electronically issued prescription obligations meets the modern requirements of the healthcare system. A digital record of the issued prescriptions aims at preventing prescriptions from being traded without a physician's name in patient medical records. Access to the system may in turn reveal doctors' bad practices, and fear of the professional and legal consequences may force a change in the prescription of benzodiazepines or non-benzodiazepine hypnotics. The effect of these activities may be the disclosure of many cases of 'hidden' dependence and adverse phenomena and increase in the number of effects of cases of sudden dose reduction or discontinuation of benzodiazepines or non-benzodiazepine hypnotics. It is recommended to develop integrated, central information and train Emergency Department staff. Awareness of the phenomenon and appropriate diagnostic and therapeutic procedures can significantly increase the chance of improving the quality and safety of services provided in the acute intervention mode (Emergency Department). A rational solution may be to urgently develop standards of conduct in cases of acute withdrawal syndromes from benzodiazepines or non-benzodiazepine hypnotics. It seems reasonable to introduce preventative programs enabling early recognition and treatment of cases where large and very large doses of drugs have been taken (high dose tolerance). Under no circumstances should medication be stopped abruptly. An information campaign, raising awareness also among the personnel of psychiatric wards, may increase the chances of systemic preparation for admission of the currently unknown population of patients at risk.

Key words: acute benzodiazepine withdrawal, e-health, e-prescriptions, non benzodiazepine hypnotics, benzodiazepines

Introduction

Starting on January 8th 2020, physicians in Poland will be obliged to use electronically issued prescriptions (Dz. U. (Journal of Laws) 2018 item 697. Dz. U. (Journal of Laws) 2019 item 1590) [1, 2]. The implementation of solutions in the area of e-health not only meets the modern requirements of the healthcare system, but also supplements this system with an access to knowledge about recently prescribed medicines, doses and number of tablets recommended.

A full digital record of the issued prescriptions aims at preventing prescriptions from being traded without a physician's name in the digital medical records. The first e-prescription pilot program took place in Sweden in the 1980s, where at present this system already covers nearly 99% of prescriptions [3]. The main assumptions for implementing e-health solutions were to increase the safety and effectiveness of healthcare. Despite the enthusiastic acceptance of these solutions, there were voices making a critical assessment of e-prescriptions [4, 5]. There is a reported risk of increase of the frequency of prescriptions (only in hospital conditions) of benzodiazepines to patients who have not taken them before [6]. Younger patients are also identified as at risk [7]. Ease of ordination and repetition of the prescribed medicine order via e-applications may play a contributing role in that. In the case of drugs from other groups, there have already been reported cases related to the consequences of not prescribing or dispensing drugs via e-prescriptions (12% of all prescribed drugs used in the treatment of internal diseases) [8]. Research reviews provided information on unintended potential consequences of using electronically prescribed prescriptions. Among the identified problems, technological ones, among others, are indicated as well as those that may potentially occur in connection with the human factor [5, 9, 10]. The development of technology in the area of e-health enables the introduction of tools that may be used to control over prescribed drugs, e.g., Clinical Decision Support (CDS). An application that allows not only the appropriate drug names to be suggested, but also the number of tablets or the dose administered over time [5].

Among the potential consequences of introducing e-prescriptions in healthcare system, it has not yet been indicated that access to the system can directly affect the behavior of doctors and pharmacists. High-risk drugs, due to long-term, often off-label use, include benzodiazepines, non-benzodiazepine hypnotics (zolpidem, zopiclone, Zaleplon) as well as analgesics from the synthetic opioid group. Some physicians may be afraid of the consequences of continuing to issue prescriptions incorrectly and will therefore start to refuse to prescribe medication in their current quantity. Other physicians, seeing the prescriptions already issued in the system, may refuse to prescribe additional packages of the drug (that applies to cases of patients visiting multiple healthcare provider entities in order to obtain the desired, but officially not declared, number of tablets). Therefore, there is a real threat that fear of professional and legal consequences may force a change in the ordinance of medicines. Finally, the data on the number of prescribed packagings will be subject to verification at the pharmacy, where the pharmacist will be able to determine, among other factors, that there were no duplicate prescriptions. In the literature, the circumstances of system failure and

the lack of legal possibility to issue a prescription outside the e-system are also ignored. A similar phenomenon has been observed in the United States with synthetic opioid drugs following the introduction of increased control over the prescription of this group of drugs. The effect of these activities was the disclosure of many cases of 'hidden' dependence and many adverse phenomena such as: an increased number of acute withdrawal syndromes, plus search on the illegal market for a substitute for legal opioids [11].

Benzodiazepines and non-benzodiazepine hypnotics

To date, no data on the prevalence of abuse and addiction to benzodiazepines or hypnotics have been published in Poland. Data from the National Health Fund (NFZ) allow monitoring prescriptions only for reimbursed drugs [12, 13]. At the same time, the picture of benzodiazepine abuse is compared to an epidemic [14].

Data from the research in the United States have shown that benzodiazepines are the third most abused substance group among legal (prescriptions) and illegal substances (street psychoactive substances), which affects more than 2% of the population. The authors of this study postulate that the data obtained in population studies from the United States correspond to the frequency of use of these drugs all over the world. However, such extrapolations should be approached with caution. It was noted that in the better part of the two most recent decades the number of visits of outpatients using benzodiazepines has doubled [15, 16].

French studies prove that the incidence of benzodiazepine long-term use (BLTU) in men was 2.8%, and among women 3.8%, and the authors themselves point out the difficulties in real estimation of the phenomenon, among others, due to methodological difficulties [17]. The results of the study confirm the observations from previous studies from France and Germany [18, 19].

A pilot study was carried out on the Polish population in which prescriptions from three pharmacies in Lesser Poland were identified, indicating that alprazolam (26%) and zolpidem (16%) were most commonly prescribed among benzodiazepines and hypnotics [12]. Attention was paid to difficulties in assessing the phenomenon of benzodiazepine and zolpidem abuse due to the lack of monitoring of the length of treatment [20] and monitoring of cases of extremely high doses of zolpidem used by patients [21, 22]. This situation leads to the fact that modern guidelines for management of people using benzodiazepines are directed to two groups: (1) people using drugs as recommended, at the 'therapeutic dose', and (2) people abusing drugs 'off label', at higher doses, as a special risk group [23]. At the same time, the need to educate doctors regarding safe use of medicines and proper treatment of addicts has been reported for years [24], which is reflected in the recently published recommendations for Polish primary care physicians [25].

An increased risk of suicide has been reported in association with the use of benzodiazepines or hypnotics, with correlations with dose, insomnia and impulsiveness secondary to drug reduction or discontinuation, i.e., acute withdrawal syndrome [26, 27], and due to possible harm associated with their use, it is recommended to discon-

tinue them after the indications for use have ceased [28]. Particular emphasis is placed on the educational value that protects against prolonged exposure to benzodiazepines in treatment and the benefits of withdrawal, alleviated by an individual approach [29]. The principles of responsible use of this group of drugs, monitoring the risk of harm and addiction, and safe withdrawal of benzodiazepines are discussed [30]. The Institute of Psychiatry and Neurology in Warsaw has been working on systematizing the drug detoxification model for years [31, 32], and the author of the method will soon publish the results of her research.

While the withdrawal methods for benzodiazepines are based primarily on the individualized and controlled management of the withdrawal syndrome under medical supervision and in psychological support, abrupt withdrawal of medications (e.g., as a result of changes in drug regulations) may increase the risk of acute and life-threatening withdrawal syndrome [33].

Precautions

In many cases, taking a medical history does not pose any major difficulties, and in the event of difficulties in contact with the patient, healthcare providers can use the interview collected from people in the patient's environment. In urgent cases, it may happen that the lack of reliable information may affect the choice of the correct procedure and, consequently, its effectiveness: the health or even the life of a patient.

Due to the existing legal circumstances and a significant likelihood of increase in the number of cases of sudden dose reduction or discontinuation benzodiazepines or non-benzodiazepine hypnotics, it is absolutely recommended to develop integrated, central information and train Emergency Department personnel, ambulance staff and Emergency Room team members.

In any clinically unclear case in which there are disturbances of consciousness of unknown causation, state after seizure, status epilepticus, quantitative disturbances of consciousness, hypertensive orifice, or similar symptomatology, drug intoxication, sudden reduction of dose or discontinuation of benzodiazepines or non-benzodiazepine hypnotics should be suspected. Some precautionary measures may be recommended:

- provide at least one access to a peripheral vein;
- blood sampling to a clot tube for laboratory quantification of serum benzodiazepines (ng/ml);
- collect urine samples for routine urine testing for opioids and benzodiazepines;
- collect urine samples in a dark container, stored in the refrigerator until transport, for toxicological qualitative research to screen for, among others: zolpidem, zopiclone, tramadol or codeine;
- attempt to contact relatives to deepen the interview.

With justified suspicion of drug withdrawal syndrome underlying the observed disorders, it seems justified to conduct:

- further diagnosis and treatment in cooperation with an anesthesiologist;
- follow the maintenance treatment in monitored conditions;
- for withdrawal seizures – intravenous administration of diazepam, lorazepam or midazolam via the pump should be considered, as in the treatment of status epilepticus [34];
- after the acute state stabilizes, consideration should be given to referring the patient to the nearest detoxification or psychiatric ward, and in the case of opioid withdrawal syndrome, transfer to the nearest drug detoxification unit should be agreed.

It should be emphasized that in the case of withdrawal syndrome from medications, as in the case of alcohol withdrawal syndromes, patients should be treated in an appropriate facility where the best care can be provided. The advantages of the treatment in psychiatric and detoxification wards are the properly trained and experienced staff and the procedures for dealing with excited and aggressive patients with impaired consciousness. However, it is recommended that the majority of withdrawal syndromes with withdrawal seizures should be treated in neurological departments, where better diagnostic possibilities, monitoring of the patient's condition and treatment are offered [35].

Recapitulation

This paper concerns hitherto overlooked difficulties in the management of acute withdrawal syndrome from benzodiazepines and non-benzodiazepine hypnotics. The current postulated and available recommendations are related to the treatment of intoxication, abuse and addiction to these drugs. It is worth emphasizing that the introduced changes in the area of e-health are mainly beneficial for the care of patients. The unintended effect of e-prescriptions on changing drug ordination is one of many potential factors that may directly or indirectly affect the occurrence of acute withdrawal syndromes from benzodiazepines and hypnotics.

The challenge for the healthcare system in Poland is to conduct epidemiological studies to describe the image of abuse and benzodiazepine addiction. Similar studies were commissioned by the Minister of Health of the United Kingdom to assess the prevalence, scale and causes of drug addiction [36].

To be able to implement adequate prevention in the area of drug addiction, it is necessary to keep a record of occurrences and monitor the events of acute withdrawal syndrome treatment in hospitals. In addition, awareness of the phenomenon and appropriate diagnostic and therapeutic procedures can significantly increase the chance of improving the quality and safety of services provided in the acute intervention mode (Emergency Departments, Emergency Rooms). A rational solution may be to urgently develop standards of conduct in cases of acute withdrawal syndromes from benzodiazepines or non-benzodiazepine hypnotics. It seems reasonable to introduce preventative programs enabling early recognition and treatment of cases of taking

large and very large doses of drugs (high dose tolerance). Under no circumstances should medication be stopped abruptly. An information campaign, raising awareness also among the personnel of psychiatric wards, may increase the chances of systemic preparation for admission of the currently unknown population of patients at risk.

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